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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,334	08/30/2001	Charles W. Rittershaus	TCS-411.1P US-1	9968

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,334	RITTERSHAUS ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,29 and 37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,29, 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 02/07/03 (Paper NO: 8), is acknowledged.

Claims 28, 29 and 37-39 re pending.

2. *Claims 28, 29 and 37-39 as they read upon elected species to a method for therapeutically or prophylactically treating atherosclerosis, comprising administrating a vaccine peptide, comprising a helper T cell epitope portion and B cell epitope portion, wherein T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid and B cell epitope portion comprises B cell epitope of CETP or method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide wherein T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid and B cell epitope portion of CETP comprises a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1 or method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide wherein vaccine peptide comprises the amino acid sequence of SEQ ID NO:2 or dimer thereof are under consideration in the instant application.*

In view of the amendment, filed 02/07/03 (Paper NO: 8) and Terminal Disclaimer, filed 02/07/03 (Paper NO: 9) only the following rejections remain:

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 28-29 and 37-39,stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating atherosclerosis, comprising administrating an antigenic vaccine peptide, comprising of the amino acid sequence of SEQ ID NO:2 or a dimer thereof or comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1 , does not reasonably provide enablement for : (A) method for preventing atherosclerosis comprising administrating *any* vaccine peptide comprising a universal helper T cell epitope portion linked to *any* B cell epitope portion of CETP, as recited in claims 28 or 29; or (B) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (C) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (D) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims essentially for the same reasons set forth in the previous Office Action, paper NO:6, mailed 07/30/02.

Applicant's arguments, filed 02/07/03 (Paper NO: 8) have been fully considered, but have not been found convincing.

Applicant asserts that by adopting the terminology of allowed claims of the US. Patent 6,410,022, the amendment claims of the instant application would obviate all of the formal rejections under first paragraph of 35 U.S.C. 112.

Contrary to Applicant assertion it is noted that the functional limitations of the present amended claims are different from functional limitations of US Patent '022 claims. For example, claim 18 of US Patent '022 recited only method of treating atherosclerosis, while the instant claim 28 recited a method of treating or preventing atherosclerosis. In addition, claim 18 of US Patent '022 recited an antigenic vaccine wherein B cell epitope portion comprises six to 26 consecutive amino acids of the carboxyl terminal 26 amino acid of human CETP (SEQ ID NO:1), while the instant claim 28 recited *any* B cell epitope of CETP.

As was stated in the Previous Office Action paper NO:6, mailed 07/30/02, the issue is whether or not the claimed method would function for preventing atherosclerosis. The nature of the invention is such that it would require the administration of vaccine peptide to prevent a mammalian subject from having atherosclerosis. However, according to Maillard et al (Presse. Med, 30, 73, 2201) there is lack in effective methods capable of preventing atherosclerosis-related conditions. (see Abstract in particular).

It is noted that Applicant does not addressed this issue.

Also , the issue was that the specification does not provide sufficient guidance as to which method for treating atherosclerosis, comprising administrating *any* vaccine peptide, comprising universal helper T cell epitope portion linked to and *any* B cell epitope of CETP, broadly encompass by the claims would have the same efficiency as method for therapeutically treating atherosclerosis, comprising administrating a vaccine peptide, comprising the amino acid sequence of SEQ ID NO:2 or a dimer thereof or comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1.

Applicant is relying upon certain biological activities and the disclosure of a limited number of species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated *any* vaccine peptide, comprising universal helper T cell epitope portion linked to and *any* B cell epitope of CETP encompassed by the claimed invention other than antigenic vaccine peptide comprising the amino acid sequence of SEQ ID NO:2 or a dimer thereof or comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1. would be expected to have greater differences in their activities.

Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. production of native antibodies that recognize the subject's own, endogenous CETP) requires a knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects the peptides and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method for preventing atherosclerosis comprising administrating *any* vaccine peptide comprising a universal helper T cell epitope portion linked to *any* B cell epitope portion of CETP, as recited in claims in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

5. Claims 28, 29 and 37-39 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention essentially for the same reasons set forth in the previous Office Action, paper NO:6, mailed 07/30/02.

Applicant's arguments, filed 02/07/03 (Paper NO: 8) have been fully considered, but have not been found convincing.

Applicant asserts that by adopting the terminology of allowed claims of the US. Patent 6,410,022, the amendment claims of the instant application would obviate all of the formal rejections under first paragraph of 35 U.S.C. 112. In addition, Applicant asserts that an adequate written description can be achieved by actual reduction to practice of treatment and prevention of atherolsclerosis using a vaccine peptide according the description.

Contrary to Applicant assertion as has been discussed supra, the factual pattern of the present amended claims is different from allowed subject matter of US Patent '022 claims.

Moreover, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize

applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention vaccine peptide comprising a universal helper T cell epitope portion linked to *any* B cell epitope portion of CETP and it's function production of native antibodies that recognize the subject's own, endogenous CETP, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed method for preventing atherosclerosis comprising administrating vaccine peptide, wherein vaccine peptide comprising a universal helper T cell epitope portion linked to *any* B cell epitope portion of CETP which retain the features essential to the instant invention.

Applicant is in possession of : a method for treating atherosclerosis, comprising administrating an antigenic vaccine peptide, comprising of the amino acid sequence of SEQ ID NO:2 or a dimer thereof or comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1.

Applicant is not in possession of : (A) method for preventing atherosclerosis comprising administrating *any* vaccine peptide comprising a universal helper T cell epitope portion linked to *any* B cell epitope portion of CETP, as recited in claims 28 or 29; or (B) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (C) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (D) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39.

Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of polypeptide sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 28-29 and 37-38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Whitlock et al. (J Clin. Invest.84:129,1 989) in view of the known fact disclosed in the specification on page 2, lines 10-12, Stevens et al.(U.S. patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992) essentially for the same reasons set forth in the previous Office Action, paper NO:6, mailed 07/30/02.

Applicant's arguments, filed 02/07/03 (Paper NO: 8) have been fully considered, but have not been found convincing.

Applicant asserts that " the Examiner has fallen into trap of hindsight reconstrustion by mentally presuming the existence of a motivation or suggestion to combine all references." Applicant also asserts that : (i) there is no teaching or suggestion in Whitlock of actively immunizing an individual against their own CETP; (ii) Stevens does not teach or suggest active immunization against a constitutively produced protein involved in cholesterol metabolism; (iii) there is no mention in Swenson of the concept of active immunization of an individual to continuously control CETP activity via an endogenous immune response; (iv) there is no mention in Valmori of a concept of actively immunizing an individual against their own CETP; (v) that Michel et al teaches that successful use of passive immunization is not predictive of active immunization; (vi) immunization against a foreign CETP has been shown in the references but active immunization against a self CETP has not and none of the references provide substantial evidence of a teaching or motivation to actively immunizing an individual against their own CETP; (vii) actual performance of this work produced an antibody response that was specific and which produced lasting effects on cholesterol and HDL levels that was unexpected.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

In addition, the amended claims encompass administration of an antigenic vaccine peptide, comprising a universal T helper cell epitope portion linked to human CETP portion to non-human. that is immunization against a foreign CETP. Claim 28 specifically indicate that said antigenic vaccine peptide can be administered to human or animal. Moreover, it is noted that at the time the invention was made active immunization against "self-antigens" that is breaking of tolerance to endogenous proteins by enhancing the immunogenicity of "self-antigen" with universal helper T cell epitope was well known in the art. Thus it would be obvious to one of ordinary skill in the art at the time the invention was made to use active immunization using self CETP. The rationale to support a rejection under 35 U.S.C. 103 may rely on logic and sound scientific principle. In re Soli , 317 F.2d 941, 137 USPQ 797 (CCPA 1963).

With respect to Applicant's arguments that Michel et al. teaches that successful use of passive immunization is not predictive of active immunization.
This argument is not persuasive in view of the prior art success in eliciting antibodies to CETP by conjugating CETP B cell epitope to carrier proteins. Moreover, Applicant 's argument that Michel et al. teaches that only 1/50 rats were antibodies elicit when immunized with pure rabbit converting enzyme is not on point, since te instantly claimed methods are not drawn to immunizing with intact CETP, but rather to conjugates of CETP B cell epitopes to carrier proteins which are known in the art to increase the efficiency of eliciting antibodies to the epitopes conjugated to the carrier protein.

With respect to Applicant's arguments that actual performance of this work produced an antibody response that was specific and which produced lasting effects on cholesterol and HDL levels that was unexpected and IE a thousand fold duration of CETP modulation as compared to method of Whitlock et al. This argument is not persuasive, since it is well known in the art that when antibodies from one species (i.e. murine monoclonal antibodies) are administered to another species (i.e. rabbit) as was done in Whitlock et al. the antibodies have a relatively short half-life as compared to antibodies elicited by administration of a vaccine. Foreign proteins such as mouse antibody in a rabbit are eliminating as foreign. Therefor the increase in duration of modulation of CETP activity using the instantly claimed methods versus the method of Whitlock et al. is not an unexpected result.

Whitlock et al., teaches that in vivo administration of CETP neutralizing antibodies leads to an elevation of circulating HDL, elevation in the ratio of circulating HDL to LDL, VLDL and total cholesterol, a decrease in the level of endogenous CETP activity and increase in the level of circulating HDL. Whitlock et al further teach that increase of HDL while decrease of VLDL would lead to decreased of LDL levels which would be beneficial for decrease in the development of atherosclerosis legions (see entire document and page 129 in particular).

The specification on page 2, lines 10-12, discloses that it is well known that increase in the level of circulating HDL is essential in therapeutically treating of atherosclerosis .

The claimed invention differs from the prior art by the recitation of using a vaccine peptide comprising T cell epitope derived from Tetanus toxoid conjugated to a B cell epitope derived from C-terminus of CETP instead of using CETP neutralizing antibodies in a method for therapeutically treating of atherosclerosis.

Swenson et al. teaches the immunogenic peptide CETP-contains a B cell epitope and that administration of this peptide into animals results in production of anti- CETP antibody (see page 14319 in particular). Swenson et al. further teaches the criticality of the carboxyl terminal 26 amino acid sequences derived from CETP, for the elicitation of antibody which decrease the level of endogenous CETP activity (see abstract and entire document). The carboxyl terminal 26

amino acid sequence of CETP is 100 % identical to SEQ ID NO: 1 of the instant application. Thus, Swenson et al. teaches a immunogenic peptide that is the exact the same length and composition as amino acid sequence of SEQ ID NO:I and the same amino acid sequence as amino acid numbers 16-31 of SEQ ID NO:2. Swenson et al. also teaches that treating of atherosclerosis in human can be generally achieved by modulating the activity of endogenous CETP (see page 14318).

Stevens et al. teaches that active administration of antigen-tetanus toxoid conjugates to induce antibody responses for therapeutic effects are advantageous over passive administration of the antibody to the antigen because passive immunization procedures cause anti-antibody responses that cause serious side effect reaction upon repeated injection of the antibody (see column 2 in particular). In addition, Stevens et al. teaches adding a c-terminus cycteine onto the antigen so it can be linked to a Tetanus toxoid peptide or other carrier. Lastly, Stevens et al. teaches the conjugation of peptides to carriers to increase the peptides immunogenicity (see Abstract particular).

Valmori et al. teaches that universally antigenic T cell epitopes (a.a. 830-843 and 947-967) derived from Tetanus Toxoid (the elected T cell epitope) can be used as carriers (helper T cell epitope) for B cell epitope and that such hybrid peptides can be used to elicit antibody production in human and mice (see Abstract and entire document). Valmori et al. also teaches tetanus toxoid peptide that is the same as amino acids 2-16 of SEQ ID NO:2 of the instant application.

Giving the teaching of Stevens et al. and Valmori et al. that active administration of antigen-toxoid conjugates elicit antibody production in human and mice and teaching of Whitlock et al. that in vivo administration of CETP neutralizing antibodies leads to an inhibition of CETP activity and increase in the levels of circulating HDL and teaching of Whitlock et al., Swenson et al. and known fact disclosed in specification on page 2 that increase in the level of circulating HDL is essential in therapeutically treating of atherosclerosis one ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to therapeutically treat atherosclerosis by administering a vaccine peptide, comprising a helper T cell epitope portion and CETP B cell epitope portion, wherein T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid and B cell epitope portion comprises B cell epitope of CETP.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a vaccine peptide comprising a helper T cell epitope portion derived from tetanus toxoid (as taught by Valmori et al. and Stevens et al.) and B cell epitope portion, comprising of carboxyl terminal 26 amino acid long CETP (as taught by Swenson et al) and use it in the method for therapeutically treating atherosclerosis because administration of such vaccine peptide would induce the generation of neutralizing antibody which would inhibit CETP activity (as taught by Whitlock et al.,) and inhibition of CETP activity would be essential in treating atherosclerosis (as taught by. Whitlock et al., the known fact disclosed in the specification on page 2 and Swenson et al).

One of ordinary skill in the art at the time the invention was made would have been motivated to create a vaccine comprising carboxyl terminal 26 amino acid long CETP –tetanus toxoid conjugate taught by the combined references of Swenson et al., Valmori et al. and Stevens et al. with the expectation that administration of such vaccine would elicit immune responses to the CETP component that would inhibit endogenous CETP activity in vivo. Inhibition of CETP activity would be expected to be useful in therapeutically treating atherosclerosis as taught by Whitlock et al. the known fact disclosed in specification on page 2 and Swenson et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. Claim 39 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Whitlock et al. (J Clin. Invest.84:129,1989) in view of the known fact disclosed in specification on page 2, lines 10-12, Stevens et al.(U.S. patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992) and further in view of Talwar et al. (Proc. Natl. Acad. Sci, 91: 8532-8536 1994) or Stanton et al. (U.S. Patent NO: 5,807552) essentially for the same reasons set forth in the previous Office Action, paper NO:6, mailed 07/30/02.

Applicant's arguments, filed 02/07/03 (Paper NO: 8) have been fully considered, but have not been found convincing.

Applicant asserts that because the combination of primary and secondary references (i.e. Whitlock et al., in view of the known fact disclosed in specification on page 2, lines 10-12, Stevens et al. Swenson et al., Valmori et al.) fails to render the method of treatment invention obvious, the disclosures of Talwar et al. or Stanton et al. with respect to dimiralization do nothing to overcome the insufficiency of the primary and secondary references.

Contrary to Applicant assertion as has been discussed supra, it is the examiner position that the combination of primary and secondary references (i.e. Whitlock et al., in view of the known fact disclosed in specification on page 2, lines 10-12, Stevens et al. Swenson et al., Valmori et al.) render the method of treatment invention obvious.

The prior art teaching differ from the claimed invention only by recitation that vaccine peptide comprises a dimer of immunogenic peptide of SEQ ID NO:2.

Talwar et al. teaches the use of tetanus toxoid as a carrier to elicit immune responses to autoantigens such as human chorionic gonadotrophin. (see page 8532 and entire document). Talwar et al. also teach that peptide vaccine may also consists of a heterospicies dimer of the alpha-subunit of ovine luteinizing hormone and the beta-subunit of hCG conjugated to either of two immunogenic carrier proteins to elicit production of autoantiboies, that specifically react with the particular endogenous protein.

Stanton et al. teaches the general advantage of vaccine, comprising multimers forms of immunogenic peptide over vaccine comprising monomer form of immunogenic peptide in both active and passive immunization (See Abstract and Column 8, line 20-25). Stanton et al. further teach that such vaccines are excellent candidates for providing immune protection for human and animals. (Column 8, line 24). Although Stanton et al. does not explicitly teaches a vaccine comprising a dimer form of immunogenic peptide, it would been obvious to one of ordinary skill in the art at the time the invention was made the advantage of using vaccine comprising more than one copy of immunogenic peptide for providing immune protection for human and animals.

Giving the teaching of Stanton et al. and Talwar et al. that vaccines comprising dimer of immunogenic peptide are excellent candidates for providing immune protection for human and animals and teaching of Stevens et al. and Valmori et al that active administration of antigen-toxoid conjugates elicit antibody production in human and mice plus teaching of Whitlock et al. that in vivo administration of CETP neutralizing antibodies leads to an inhibition of CETP activity and increase in the levels of circulating HDL and teaching of Whitlock et al., Swenson et al. and known fact disclosed in specification on page 2 that increase in the level of circulating HDL is essential in therapeutically treating of atherosclerosis one ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to use a vaccine peptide, comprising a helper T cell epitope portion and CETP B cell epitope portion, wherein T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid and B cell epitope portion comprises B cell epitope of CETP in the method of therapeutically treating atherosclerosis

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to construct a vaccine comprising a dimer of immunogenic peptide which will providing immune protection for human and animals (as taught by Talwar et al. and Stanton et al.) wherein said immunogenic peptide comprising a helper T cell epitope portion derived from tetanus toxoid (as taught by Valmori et al.) and B cell epitope portion, comprising of carboxyl terminal 26 amino acid long CETP (as taught by Swenson et al) with the expectation that administration of such vaccine would induce the generation of neutralizing antibody which would inhibit CETP activity (as taught by Whitlock et al.,) and that inhibition of CETP activity would be essential in treating atherosclerosis (as taught by. Whitlock et al., the known fact disclosed in the specification on page 2 and Swenson et al).

One of ordinary skill in the art at the time the invention was made would have been motivated to create a vaccine which will providing immune protection for human and animals comprising a dimer of immunogenic peptide (as taught by Talwar et al. and Stanton et al.) wherein said immunogenic peptide comprising carboxyl terminal 26 amino acid long CETP –tetanus toxoid conjugate taught by the combined references of Swenson et al., and Valmori et al. with the expectation that administration of such vaccine would elicit immune responses to the CETP component that would inhibit endogenous CETP activity in vivo. Inhibition of CETP activity would be expected to be useful in therapeutically treating atherosclerosis as taught by Whitlock et al. the known fact disclosed in specification on page 2 and Swenson et al.

9. No claim allowed

10. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
April 21, 2003.

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
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